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(FILE 'HOME' ENTERED AT 13:09:36 ON 22 APR 2002)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF' ENTERED AT 13:09:45 ON 22 APR 2002 756977 S CHROMOSOME? L1 301 S L1 AND (INTRON? (L) ENDONUCLEASE?) L2137 DUP REM L2 (164 DUPLICATES REMOVED) L3 137 FOCUS L3 1-L4 153 S L1 AND ((GROUP I INTRON?) OR (INTRON ENCODED)) L5 77 S L5 (L) ENDONUCLEASE? L6 77 S L5 AND ENDONUCLEASE? L7 37 DUP REM L7 (40 DUPLICATES REMOVED) L837 SORT L8 PY L9 37 FOCUS L9 1-L10 2 S L9 AND MAMMAL? L11FILE 'STNGUIDE' ENTERED AT 13:25:50 ON 22 APR 2002 FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF' ENTERED AT 13:26:24 ON 22 APR 2002 214 S L1 AND (I-SCEI? OR I-CSMI? OR I-PANI? OR I-TEVI? OR I-PPOI?) L12 82 DUP REM L12 (132 DUPLICATES REMOVED) L13 82 FOCUS L13 1-T.14 25 S L13 AND MAMMAL? L1525 SORT L15 PY L16 => d an ti so au ab pi 114 1 9 11 12 16 L14 ANSWER 1 OF 82 CAPLUS COPYRIGHT 2002 ACS 1998:545391 CAPLUS 129:172448 DN Cloning and expression of gene for restriction endonuclease I-SceI of Saccharomyces cerevisiae and use of I-U.S., 79 pp. Cont.-in-part of U.S. 5,474,896. CODEN: USXXAM Dujon, Bernard; Choulika, Andre; Perrin, Arnaud; Nicolas, Jean-francois IN A mitochondrial gene encoding restriction endonuclease I-SceI of Saccharomyces cerevisiae and a synthetic universal code encoding I-SceI for the expression in Escherichia coli and yeast are provided. Applications of I-SceI for genetically mapping yeast chromosomes by the nested chromosomal fragmentation strategy, inducing double stranded DNA break, and in vivo site-directed insertion of genes and homologous recombination in eukaryotes are also described. It may also be used for prepg. transgenic animal models of human diseases and genetic disorders. PATENT NO. KIND DATE APPLICATION NO. DATE ----US 1994-336241 19941107 Α 19980811 PΙ US 5792632 US 1992-971160 19921105 US 5474896 Α 19951212 US 1995-465273 19950605 US 5866361 Α 19990202 CA 1995-2203569 19951106 AA 19960517 CA 2203569 19960517 WO 1995-EP4351 19951106 WO 9614408 A2 19960829 WO 9614408 Α3 W: CA, JP RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE EP 1995-938418 19951106 A1 19970827 EP 791058 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE JP 1995-515058 19951106 JP 10508478 T2 19980825 19990907 US 1998-119024 US 5948678 Α L14 ANSWER 9 OF 82 MEDLINE MEDLINE AN 95140628

Repair of a specific double-strand break generated within a mammalian chromosome by yeast endonuclease I-SceI.

NUCLEIC ACIDS RESEARCH, (1994 Dec 25) 22 (25) 5649-57. SO Journal code: O8L; 0411011. ISSN: 0305-1048.

Lukacsovich T; Yang D; Waldman A S AU

SK1636

We established a mouse Ltk- cell line that contains within its genome a herpes simplex virus thymidine kinase gene (tk) that had been disrupted by the insertion of the recognition sequence for yeast endonuclease I -SceI. The artificially introduced 18 bp I-SceI recognition sequence was likely a unique sequence in the genome of the mouse cell line. To assess whether an induced double-strand break (DSB) in the genomic tk gene would be repaired preferentially by gene targeting or non-homologous recombination, we electroporated the mouse cell line with endonuclease I-SceI alone, one of two different gene targeting constructs alone, or with I-SceI in conjunction with each of the two targeting constructs. Each targeting construct was, in principle, capable of correcting the defective genomic tk sequence via homologous recombination. tk+ colonies were recovered following electroporation of cells with I-SceI in the presence or absence of a targeting construct. Through the detection of small deletions at the I-SceI recognition sequence in the mouse genome, we present evidence that a specific DSB can be introduced into the genome of a living mammalian cell by yeast endonuclease I-SceI. We further report that a DSB in the genome of a mouse Ltk- cell is repaired preferentially by non-homologous end-joining rather than by targeted homologous recombination with an exogenous donor sequence. The potential utility of this system is discussed.

L14 ANSWER 11 OF 82 MEDLINE

AN 92123196 MEDLINE

- TI Complex recognition site for the group I intron-encoded endonuclease I-SceII.
- SO MOLECULAR AND CELLULAR BIOLOGY, (1992 Feb) 12 (2) 716-23. Journal code: NGY; 8109087. ISSN: 0270-7306.
- AU Wernette C; Saldanha R; Smith D; Ming D; Perlman P S; Butow R A
- We have characterized features of the site recognized by a double-stranded DNA endonuclease, I-SceII, encoded by intron 4 alpha of the yeast mitochondrial COX1 gene. We determined the effects of 36 point mutations on the cleavage efficiency of natural and synthetic substrates containing the Saccharomyces capensis I-SceII site. Most mutations of the 18-bp I-SceII recognition site are tolerated by the enzyme, and those mutant sites are cleaved between 42 and 100% as well as the wild-type substrate is. Nine mutants blocked cleavage to less than or equal to 33% of the wild-type, whereas only three point mutations, G-4----C, G-12----T, and G-15----C, block cleavage completely. Competition experiments indicate that these three substrates are not cleaved, at least in part because of a marked reduction in the affinity of the enzyme for those mutant DNAs. About 90% of the DNAs derived from randomization of the nucleotide sequence of the 4-bp staggered I-SceII cleavage site are not cleaved by the enzyme. I-SceII cleaves cloned DNA derived from human chromosome 3 about once every 110 kbp. The I-SceII recognition sites in four randomly chosen human DNA clones have 56 to 78% identity with the 18-bp site in yeast mitochondrial DNA; they are cleaved at least 50% as well as the wild-type mitochondrial substrate despite the presence of some substitutions that individually compromise cleavage of the mitochondrial substrate. Analysis of these data suggests that the effect of a given base substitution in I-SceII cleavage may depend on the sequence at other positions.

L14 ANSWER 12 OF 82 CAPLUS COPYRIGHT 2002 ACS

- AN 2000:553718 CAPLUS
- DN 133:160582
- TI Gene repair involving homologous recombination induced by in vivo double-stranded cleavage of targeting DNA mediated by chimeric restriction endonuclease
- SO PCT Int. Appl., 38 pp.

CODEN: PIXXD2

- IN Choulika, Andre; Mulligan, Richard C.
- AB Methods of modifying, repairing, attenuating and inactivating a gene or other chromosomal DNA in a cell through chimeric restriction endonuclease (or meganuclease)-induced homologous recombination are disclosed. 101The method is exemplified by introducing into a cell a vector contg. a targeting DNA homologous to a chromosomal target sites and is flanked by

specific sites for restriction endonuclease I-SceI (a Saccharomyces cerevisiae intron-encoded rare-cutter endonuclease recognizing 18-bp sequence) or meganuclease, and cDNA encoding I -SceI or meganuclease. The I-SceI site is recognized and cleaved in vivo to relase the repair matrix and induce homologous recombination. The method has applications in treating or prophylaxis of a genetic disease in an individual in need.

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 2000046386 A2 20000810 WO 2000-US3014 20000203 WO 2000046386 A3 20001214

W: AU, CA, JP, US

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

EP 1147209 A2 20011024 EP 2000-908499 20000203 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

L14 ANSWER 16 OF 82 MEDLINE

AN 95198715 MEDLINE

- TI Induction of homologous recombination in mammalian chromosomes by using the I-SceI system of Saccharomyces
- SO MOLECULAR AND CELLULAR BIOLOGY, (1995 Apr) 15 (4) 1968-73. Journal code: NGY; 8109087. ISSN: 0270-7306.

AU Choulika A; Perrin A; Dujon B; Nicolas J F

The mitochondrial intron-encoded endonuclease I-SceI AB of Saccharomyces cerevisiae has an 18-bp recognition sequence and, therefore, has a very low probability of cutting DNA, even within large genomes. We demonstrate that double-strand breaks can be initiated by the I-SceI endonuclease at a predetermined location in the mouse genome and that the breaks can be repaired with a donor molecule homologous regions flanking the breaks. This induced homologous recombination is approximately 2 orders of magnitude more frequent than spontaneous homologous recombination and at least 10 times more frequent than random integration near an active promoter. As a consequence of induced homologous recombination, a heterologous novel sequence can be inserted at the site of the break. This recombination can occur at a variety of chromosomal targets in differentiated and multipotential cells. These results demonstrate homologous recombination involving chromosomal DNA by the double-strand break repair mechanism in mammals and show the usefulness of very rare cutter endonucleases, such as I-SceI, for designing genome rearrangements.

=> d an ti so au ab pi 116 2 4 5 8

L16 ANSWER 2 OF 25 MEDLINE

AN 95140628 MEDLINE

- TI Repair of a specific double-strand break generated within a mammalian chromosome by yeast endonuclease I-
- SO NUCLEIC ACIDS RESEARCH, (1994 Dec 25) 22 (25) 5649-57.
 Journal code: O8L; 0411011. ISSN: 0305-1048.

AU Lukacsovich T; Yang D; Waldman A S

We established a mouse Ltk- cell line that contains within its genome a AB herpes simplex virus thymidine kinase gene (tk) that had been disrupted by the insertion of the recognition sequence for yeast endonuclease I -SceI. The artificially introduced 18 bp I-SceI recognition sequence was likely a unique sequence in the genome of the mouse cell line. To assess whether an induced double-strand break (DSB) in the genomic tk gene would be repaired preferentially by gene targeting or non-homologous recombination, we electroporated the mouse cell line with endonuclease I-SceI alone, one of two different gene targeting constructs alone, or with I-SceI in conjunction with each of the two targeting constructs. Each targeting construct was, in principle, capable of correcting the defective genomic tk sequence via homologous recombination. tk+ colonies were recovered following electroporation of cells with I-SceI in the presence or absence of a targeting construct. Through

the detection of small deletions at the I-SceI recognition sequence in the mouse genome, we present evidence that a specific DSB can be introduced into the genome of a living mammalian cell by yeast endonuclease I-SceI.

We further report that a DSB in the genome of a mouse Ltk- cell is repaired preferentially by non-homologous end-joining rather than by targeted homologous recombination with an exogenous donor sequence. The potential utility of this system is discussed.

L16 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2002 ACS

AN 1995:534146 CAPLUS

DN 123:134052

- TI The yeast I-SceI meganuclease induces site-directed chromosomal recombination in mammalian cells
- SO C. R. Acad. Sci., Ser. III (1994), 317(11), 1013-9 CODEN: CRASEV; ISSN: 0764-4469
- AU Choulika, Andre; Perrin, Arnaud; Dujon, Bernard; Nicolas, Jean-Francois
- Double-strand breaks in genomic DNA stimulate recombination. Until now it was not possible to induce in vivo site-directed double-strand breaks in a mammalian chromosomal target. In this article the authors describe the use of I-SceI meganuclease, a very rare cutter yeast endonuclease, to induce site-directed double-strand breaks mediated recombination. The results demonstrate the potential of the I-SceI system for chromosome manipulation in mammalian cells.
- L16 ANSWER 5 OF 25 MEDLINE
- AN 95198715 MEDLINE
- TI Induction of homologous recombination in mammalian chromosomes by using the I-SceI system of Saccharomyces cerevisiae.
- SO MOLECULAR AND CELLULAR BIOLOGY, (1995 Apr) 15 (4) 1968-73.

 Journal code: NGY; 8109087. ISSN: 0270-7306.
- AU Choulika A; Perrin A; Dujon B; Nicolas J F
- The mitochondrial intron-encoded endonuclease I-SceI AB of Saccharomyces cerevisiae has an 18-bp recognition sequence and, therefore, has a very low probability of cutting DNA, even within large genomes. We demonstrate that double-strand breaks can be initiated by the I-SceI endonuclease at a predetermined location in the mouse genome and that the breaks can be repaired with a donor molecule homologous regions flanking the breaks. This induced homologous recombination is approximately 2 orders of magnitude more frequent than spontaneous homologous recombination and at least 10 times more frequent than random integration near an active promoter. As a consequence of induced homologous recombination, a heterologous novel sequence can be inserted at the site of the break. This recombination can occur at a variety of chromosomal targets in differentiated and multipotential cells. These results demonstrate homologous recombination involving chromosomal DNA by the double-strand break repair mechanism in mammals and show the usefulness of very rare cutter endonucleases, such as I -SceI, for designing genome rearrangements.
- L16 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2002 ACS
- AN 1996:428575 CAPLUS
- DN 125:107019
- TI Nucleotide sequence encoding yeast enzyme I-SceI and its use in inducing homologous recombination in eukaryotic cells and protein production in transgenic animals
- SO PCT Int. Appl., 122 pp. CODEN: PIXXD2
- IN Choulika, Andre; Perrin, Arnaud; Dujon, Bernard; Nicolas, Jean-Francois
- AB Synthetic DNA encoding the enzyme I-SceI is provided.

 The DNA sequence can be incorporated in cloning and expression vectors, transformed cell lines and transgenic animals. The vectors are useful in gene mapping and site-directed insertion of genes. A synthetic gene encoding Saccharomyces cerevisiae I-SceI restriction endonuclease was expressed in Escherichia coli and yeast. The enzyme was used in genetic mapping of a yeast chromosome, of YAC's, and of cosmids. I-SceI efficiently induced double-stranded breaks in a chromosomal target in mammalian cells and the breaks

	were repaired using a donor mol. that shares homol. with the regions flanking the break.				
	PATENT NO. KIND DATE APPLICATION NO. DATE				
PI	WO 9614408 A2 19960517 WO 1995-EP4351 19951106 WO 9614408 A3 19960829				
	W: CA, JP RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5792632 A 19980811 US 1994-336241 19941107				
	EP 791058 A1 19970827 EP 1995-938418 19951106 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, S	ŝΕ			
	JP 10508478 T2 19980825 JP 1995-515058 19951106				

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(FILE 'HOME' ENTERED AT 13:09:36 ON 22 APR 2002) FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF' ENTERED AT 13:09:45 ON 22 APR 2002 1.1 756977 S CHROMOSOME? 301 S L1 AND (INTRON? (L) ENDONUCLEASE?) L2137 DUP REM L2 (164 DUPLICATES REMOVED) L3 137 FOCUS L3 1-Ľ4 153 S L1 AND ((GROUP I INTRON?) OR (INTRON ENCODED)) L5 77 S L5 (L) ENDONUCLEASE? L6 77 S L5 AND ENDONUCLEASE? L7 37 DUP REM L7 (40 DUPLICATES REMOVED) L837 SORT L8 PY L9 37 FOCUS L9 1-L10 2 S L9 AND MAMMAL? L11 => d an ti so au ab 111 1-2 L11 ANSWER 1 OF 2 MEDLINE MEDLINE 95198715 Induction of homologous recombination in mammalian ΤT chromosomes by using the I-SceI system of Saccharomyces MOLECULAR AND CELLULAR BIOLOGY, (1995 Apr) 15 (4) 1968-73. SO Journal code: NGY; 8109087. ISSN: 0270-7306. Choulika A; Perrin A; Dujon B; Nicolas J F ΑU The mitochondrial intron-encoded endonuclease ΑB

I-SceI of Saccharomyces cerevisiae has an 18-bp recognition sequence and, therefore, has a very low probability of cutting DNA, even within large genomes. We demonstrate that double-strand breaks can be initiated by the I-SceI endonuclease at a predetermined location in the mouse genome and that the breaks can be repaired with a donor molecule homologous regions flanking the breaks. This induced homologous recombination is approximately 2 orders of magnitude more frequent than spontaneous homologous recombination and at least 10 times more frequent than random integration near an active promoter. As a consequence of induced homologous recombination, a heterologous novel sequence can be inserted at the site of the break. This recombination can occur at a variety of chromosomal targets in differentiated and multipotential cells. These results demonstrate homologous recombination involving chromosomal DNA by the double-strand break repair mechanism in mammals and show the usefulness of very rare cutter endonucleases, such as I-SceI, for designing genome rearrangements.

L11 ANSWER 2 OF 2 CANCERLIT

AN 96605697 CANCERLIT

TI Repair of DNA double strand breaks in mammalian cells by homologous recombination and end-joining mechanisms (Meeting abstract).

SO J Cell Biochem, (1995). Suppl. 21A, pp. 328. ISSN: 0730-2312.

AU Jasin M; Rouet P; Smih F

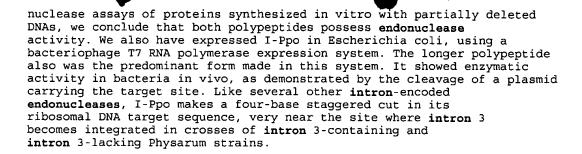
To study the repair of DSBs introduced into mammalian chromosomal DNA, we have developed expression vectors for rare-cutting, site-specific endonucleases from S cerevisiae. We used the universal code equivalent of the mitochondrial intronencoded endonuclease I-Sce I to build the mammalian expression vector, pCMV-I-Sce I. The I-Sce I sequence was provided by B Dujon, Pasteur Institute. In addition to providing a consensus Kozak sequence for efficient translation, the I-Sce I ORF was modified by fusing sequences encoding a nuclear localization signal and a hemagglutinin epitope tag. Our initial assay for in vivo cutting and enhanced recombination measures extrachromosomal recombination, since this form of recombination is very efficient in mammalian cells and sensitive to DSBs. The assay utilizes RSVCAT plasmid substrates consisting of overlapping chloramphenical acetyltransferase (CAT) gene fragments transiently transfected into cells. The RSVCAT plasmids were modified by the insertion of a synthetic I-Sce I site at the end of the homology repeats and cotransfections were carried out in COS 1 cells. We observed a substantial increase of CAT activity in cotransfections of pCMV-I-Sce I

with CAT substrates containing the I-Sce I site but not with plasmids lacking the site. Southern analysis verified in vivo cleavage, as well as recombination. Constitutive expression of the endonuclease is not toxic to mouse 3T3 cells. These results have been recently published (Rouet P et al, Proc Natl Acad Sci; 91:6064 1994). We have recently observed efficient cutting of introduced chromosomal I-Sce I sites in 3T3 cells and have found that they are recombinogenic, stimulating gene targeting two to three orders of magnitude. However, they are also repaired efficiently by end-joining mechanisms (Rouet P et al, Mol Cell Biol, in press). Results of these studies were presented. It is expected that expression of rare-cutting endonucleases in mammalian cells will provide a powerful tool for the analysis of the repair of chromosomal DSBs, as well as for molecular genetic manipulations, such as chromosome fragmentation and, potentially, gene-targeting.

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     ANSWER 1 OF 137 CAPLUS COPYRIGHT 2002 ACS
     1994:318316 CAPLUS
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     120:318316
     Thermostable sequence-specific endonucleases of Desulfurococcus and
ΤI
     Pyrobaculum, genes encoding them, and their use in gene analysis and
SO
     PCT Int. Appl., 73 pp.
     CODEN: PIXXD2
     Dalgaard, Jacob Zeuthen; Garrett, Roger Antony; Kjems, Joergen
IN
     Thermostable sequence-specific DNA endonucleases are encoded by
AΒ
     archael type introns of stable RNA (rRNA or tRNA) or protein
     genes or are enzymically active variants thereof in which one or more
     amino acid residues have been deleted, inserted or substituted by other
     amino acids. These endonucleases recognize relatively long
     sequences of about 20 base pairs and are very rare cutters, cleaving with
     a frequency of about 1:5,000,000. Thus, they are useful as endonuclease tools for gene anal., such as genome mapping and
     detection of major rearrangements in large genomes, and for gene
     manipulation, such as cloning and chromosome targeting. Two
     protein-encoding introns were discovered in the 23S
     rRNA-encoding gene of P. organotrophum. The RNA products circularize after excision from the 23S rRNA and are stable in the cell. The putative
     proteins encoded by the introns contain a common decapeptide
     sequence which is shared by the putative proteins encoded by both the
     archael intron of D. mobilis and many group I introns.
     The intron of D. mobilis was shown to encode an
     endonuclease, the active form of which could be expressed from the
     linear or cyclized intron, but not from the pre-rRNA.
     Endonucleases from P. organotrophum (I-Por I) and from D. mobilis
     (I-Dom I) were produced with recombinant Escherichia coli and their
     homing/cleavage sites detd.
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                       Al 19940303
                                            WO 1993-DK264
PΤ
     WO 9404663
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             KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD,
             SE, SK, UA, US, VN
         RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
     ANSWER 7 OF 137
                          MEDLINE
L4
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AN
     90287128
     Characterization of I-Ppo, an intron-encoded
ΤI
     endonuclease that mediates homing of a group I intron in
     the ribosomal DNA of Physarum polycephalum.
SO
     MOLECULAR AND CELLULAR BIOLOGY, (1990 Jul) 10 (7) 3386-96.
     Journal code: NGY; 8109087. ISSN: 0270-7306.
ΑU
     Muscarella D E; Ellison E L; Ruoff B M; Vogt V M
AB
     A novel and only recently recognized class of enzymes is composed of the
     site-specific endonucleases encoded by some group I
     introns. We have characterized several aspects of I-Ppo, the
     endonuclease that mediates the mobility of intron 3 in
     the ribosomal DNA of Physarum polycephalum. This intron is
     unique among mobile group I introns in that it is located in
     nuclear DNA. We found that I-Ppo is encoded by an open reading frame in
     the 5' half of intron 3, upstream of the sequences required for
     self-splicing of group I introns. Either of two AUG initiation
     codons could start this reading frame, one near the beginning of the
     intron and the other in the upstream exon, leading to predicted
     polypeptides of 138 and 160 amino acid residues. The longer polypeptide
     was the major form translated in vitro in a reticulocyte extract. From
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7 N	Hits	Search Text	DB	Time stamp
L Number	360	(group ADJ I ADJ Intron)or (intron ADJ	USPAT;	2002/04/22 13:49
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			DERWENT; USOCR	